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Restless leg syndrome in pregnancy

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Abstract

Restless leg syndrome, more recently renamed Willis-Ekbom disease, is a condition that disrupts sleep and occurs more frequently in the pregnant population. We present a 39-year-old woman with restless legs syndrome in the third trimester and discuss the epidemiology, pathophysiology and therapeutic options in the pregnant population while highlighting the challenges posed by the lack of safety data of approved drugs.

Keywords

Restless leg syndrome, pregnancy, sleep, Willis-Ekbom disease

Case presentation

Our patient was a 39-year-old woman Gravida 1 Para 0 at 35 weeks gestation whom we evaluated after she spoke with her OB/GYN about 'aching legs at night'. She was in good health otherwise and had no issues with her pregnancy. The patient complained that her legs were aching when she went to bed at night beginning around the sixth month of pregnancy, and the aching had worsened during the past several weeks. She reported no symptoms during the daytime, even when sitting still. She had massaged them and finally resorted to using a rolling pin for relief which helped for a short period of time. Occasionally, the aching would prevent her from falling asleep even though she was very tired. She otherwise had an uncomplicated pregnancy, but did complain of some fatigue and dyspnea with exertion. Physical examination findings were all within normal limits. Laboratory studies revealed haemoglobin of 7 g/dl (normal > 10.5 g/dl).

Introduction

Sleep complaints are quite common during pregnancy. For some women, the changes in body size and shape are part of the problem, but for others the complaints are very specific. In the case, we discuss, this patient complained of aching in her legs at bedtime and felt relief by movement or massage. This is consistent with a diagnosis of restless leg syndrome (RLS) or under the new name of Willis-Ekbom disease (WED). The first known medical description of restless legs occurred in 1672 by an English physician, Sir Thomas Willis, who wrote that those affected were '…no more able to sleep, than if they were in a place of greatest torture…'[1] The earliest description in modern medical literature is by Karl-Axel Ekbom in 1945, and he labelled it as a 'restless leg' condition. He described the symptoms and identified pregnancy as a common cause.[2,3] In 1980, Coleman was the first to detail the condition by characterising limb movements based on their periodicity, duration and persistence during sleep.[4] Eventually, two conditions that have similar pathophysiology and treatments were identified, described and separated into RLS and periodic limb movement disorder (PLMD).[5] Pregnancy is listed as a risk factor for developing the RLS and PLMD. Much of the available scientific literature focusses on RLS and its association with pregnancy. PLMD has an 80–90% association with RLS; however, PLMD is a separate entity that can be also associated with narcolepsy and Parkinson disease. There is very little data on PLMD in pregnancy and this paper will therefore focus on RLS and pregnancy.

RLS definition

RLS is a condition of unpleasant leg sensations that typically occur prior to sleep onset and cause an almost irresistible urge to move the legs.[5] It is considered a sensorimotor disorder with the sensory component as the urge to move the legs and the motor component is that movement of the legs often abolishes the discomfort or relieves the urge to move. Table 1 shows the four necessary diagnostic features required for the diagnosis of RLS, and Table 2 shows the most commonly associated features that may also be present. The symptoms in Table 2 are not necessary to make the diagnosis of RLS.[6]

Most patients report the first feature as some type of urge to move their legs and an unpleasant sensation such as pain, restlessness, tingling, burning, aching, or creeping feeling.[7] The second feature is simply that the urge to move and the unpleasant sensation typically occur when the patient is ready to fall asleep or is sedentary. These symptoms can increase as the duration of inactivity increases.[5] The third feature is that the urge to move the legs or the unpleasant sensation in the legs is partially or completely abolished when movement of the legs occurs. Massaging the legs or feet can help alleviate the symptoms as it did in the patient described. However, the relief of the symptoms only lasts as long as that massaging or movement continues.[6] The fourth and final feature is that the symptoms have a circadian pattern, meaning that they get worse during the evening or night. The patient must have all four features to make the diagnosis of RLS.

RLS epidemiology and diagnosis

For the general population in the United States, the prevalence of RLS is estimated at 5–15% and does not have any gender difference.[3,8] Interestingly, in pregnancy, the prevalence is estimated at 12–20%.[2,9] When RLS occurs during pregnancy, it is classified as transient or secondary RLS. Although unlikely, a patient could have idiopathic RLS that is noted first during pregnancy but that is uncommon. The symptoms and diagnostic criteria are the same for both idiopathic and secondary RLS (see Table 1). Secondary RLS is associated with iron

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Table 1. Required diagnostic criteria for restless legs syndrome.[6]

1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs (sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs)
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting
3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues
4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night (when symptoms are very severe, the worsening at night may not be noticeable but must have been previously present

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Table 2. Supportive clinical features of restless legs syndrome.[6]

1. Family history
   The prevalence of RLS among first-degree relatives of people with RLS is three to five times greater than in people without RLS.
2. Response to dopaminergic therapy
   Nearly all people with RLS show at least an initial positive therapeutic response to either L-dopa or a dopamine-receptor agonist at doses considered to be very low in relation to the traditional doses of these medications used for the treatment of Parkinson disease. This initial response is not, however, universally maintained.
3. Periodic limb movements (during wakefulness or sleep)
   Periodic limb movements in sleep (PLMS) occur in at least 85% of people with RLS; however, PLMS also commonly occur in other disorders and in the elderly. In children, PLMS are much less common than in adults.

Note: RLS: restless leg syndrome.
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deficiency, folate deficiency, peripheral neuropathy, end-stage renal disease, pregnancy, Parkinson's disease, rheumatoid arthritis, fibromyalgia, and several other rare causes.

RLS is diagnosed based on clinical history from the patient. Other conditions that occur during pregnancy can mimic or be misdiagnosed as RLS such as nocturnal leg cramps and hypnic (hypnagogic) jerks. Nocturnal leg cramps are very painful and sustained contractions of the gastrocnemius and soleus muscles.[10] These leg cramps can be relieved with stretching and massaging the involved leg but unlike RLS, do not resolve with movement. Hypnic jerks are an involuntary twitch which occurs just as a person is beginning to fall asleep, often causing them to awaken suddenly for a moment. Like RLS, they may also occur around sleep onset, but are not associated with the urge to move the legs nor are they relieved with movement.[5]

Pathophysiology

Although the RLS symptoms in pregnancy are almost exactly the same as idiopathic RLS, the cause may not be the same. Folate, an important cofactor for many biochemical pathways including DNA synthesis, needs to be supplemented during pregnancy due to increased requirements. Botez and Lambert described a significant relationship between RLS symptoms and folate supplementation in a study of 21 pregnant women.[11] In another study examining the longitudinal relationship of sleep patterns in healthy subjects before, during and after pregnancy, the authors found the prevalence of RLS to be 13% (4/32) in the first trimester, 18% (6/33) in the second trimester, 23% (7/30) in the third trimester, 3% (1/31) in the four weeks postpartum. The mean serum folate during the third trimester was lower for RLS group compared with the non-RLS group. Furthermore, the number of nights experiencing RLS symptoms in the third trimester correlated inversely with serum folate levels. Most interestingly, the serum folate level of all subjects was within normal limits and there were no differences in the serum ferritin level, iron, vitamin B12, or anemia indices.[12]

Dopaminergic insufficiency, specifically reduced iron in the central neurons, is another possible reason for an increased incidence of RLS during pregnancy. Manconi et al. reported on 606 pregnant women who were interviewed two days postpartum for a history of iron and folate intake. They report a prevalence rate of RLS of 26.6% for the entire group and 16.6% were newly diagnosed. Hemoglobin level was lower in the new RLS group compared to healthy control group.[13]

Other factors that may precipitate RLS symptoms include hormonal changes. Progesterone is known to increase neuronal activity and increase the respiratory centre sensitivity to carbon dioxide. This hyperexcitability may bring about PLMD or RLS. Prolactin, secreted during pregnancy, decreases dopamine action and thus could lead to increased RLS symptoms (dopaminergic insufficiency hypothesis). Interestingly, prolactin has the same circadian rhythmicity as RLS symptoms. Hormonal changes as a possible cause of RLS is supported by the finding that postdelivery, RLS symptoms resolve for the majority of patients.

Clinical and polysomnographic evaluation

RLS is a clinical diagnosis with well-established diagnostic criteria (Table 1) and a sleep study is not required. In a patient such as we describe it is important to screen for potentially treatable illnesses that may cause or exacerbate RLS such as caffeine intake (see Figure 1). Although our patient did not have it, daytime sleepiness can be a major symptom. In pregnancy, many women complain of sleepiness or fatigue and RLS could be overlooked as a cause. Laboratory evaluation recommendations include iron panel, folate, vitamin B12, thyroid function, anemia indexes, glycemic response, and renal function. Some over the counteragents may have antidopaminergic activities such as the older antihistamines. Physical examination may help distinguish imitators of RLS as described above.

Treatment

Once a diagnosis of RLS is made, treatment should be aimed at reducing or eliminating symptoms. Patients should reduce exposure from known RLS triggers such as caffeine, smoking, poor sleep

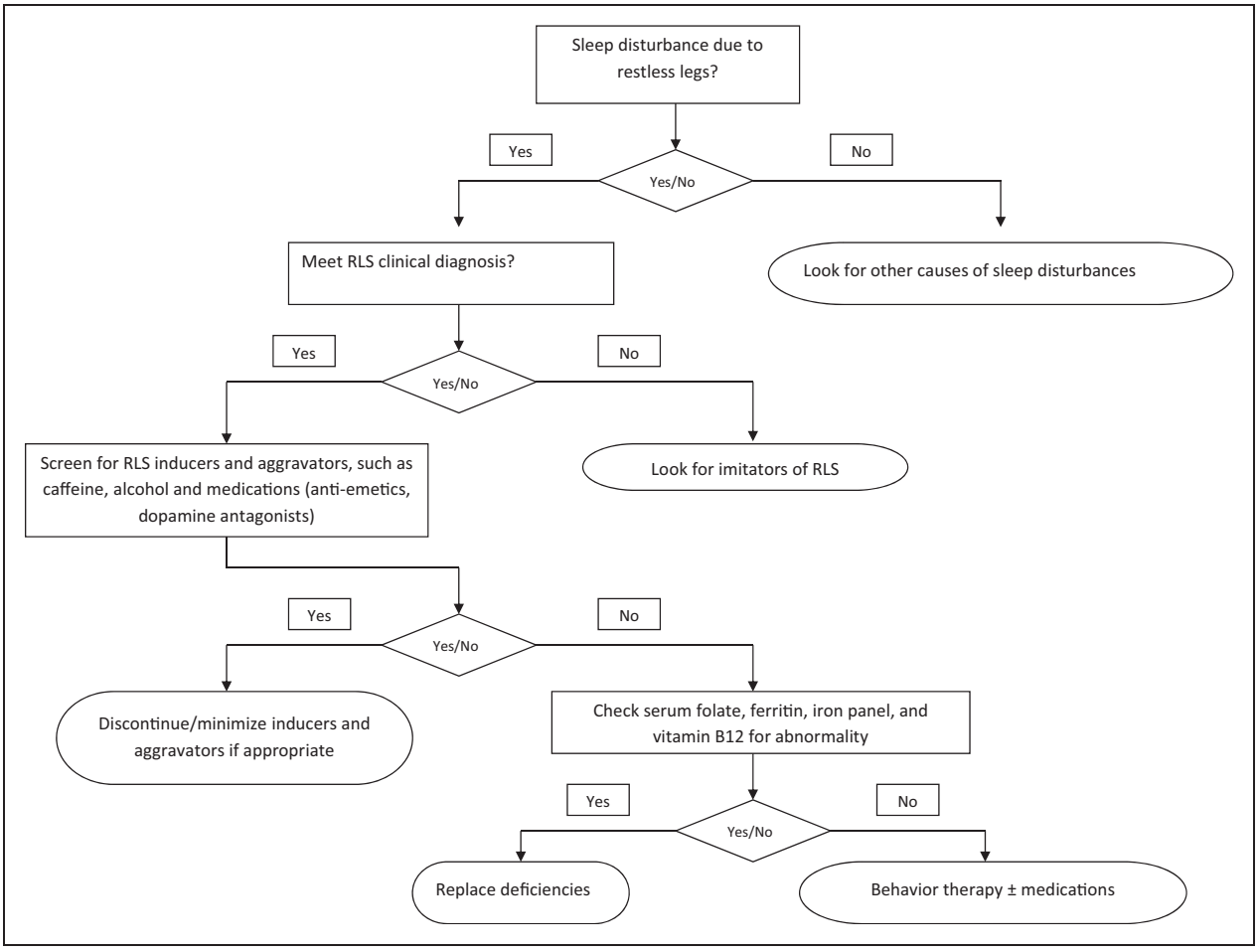

Figure 1. Screening and evaluation.

Table 3. Selected medications used in treatment of RLS in pregnancy and lactation.

Medications		Safety in pregnancy	Safety in lactation
Antiepileptic	Carbamazepine	Use during early pregnancy has been associated with an increased risk of neural tube defects and possibly an increased risk of craniofacial abnormalities and developmental delay.[14] Potential benefit in RLS may not outweigh the risk of fetal malformations	Breastfeeding during carbamazepine monotherapy does not appear to adversely affect infant growth or development. Most infants have had no adverse reactions, but sedation, poor sucking, withdrawal reactions and three cases of hepatic dysfunction have been reported[15]
	Gabapentin	There are case reports of normal pregnancy outcomes after gabapentin therapy, but there are also reports of malformations. It is not known if the risk of malformations in increased with this medication.[14] Potential benefit in RLS may not outweigh the risk of fetal malformations	Infant plasma levels following exposure through breastfeeding are probably too low to cause untoward effects in the breastfed infant.[17] Monitor the infant for drowsiness, adequate weight gain and developmental milestones, especially in younger, exclusively breastfed infants[15]
Benzodiazepine	Clonazepam	Maternal use is not thought to increase the risk of congenital malformations. Risk of transient respiratory distress and hypotonia in women taking clonazepam in combination with paroxetine[14]	Maternal clonazepam occasionally causes sedation in their breastfed infants, especially when given with other central nervous system depressants. Monitor the infant for drowsiness, adequate weight gain and developmental milestones, especially in younger, exclusively breastfed infants and when using combinations of psychotropic drugs[15]

(continued)

Table 3. Continued.

Medications		Safety in pregnancy	Safety in lactation
Dopaminergics	Levodopa	Levodopa produces adverse pregnancy outcome in experimental animals after high-dose treatment.[14] Theoretical concern about placental perfusion with Levodopa.[21] Potential benefit in RLS does not outweigh the pregnancy risk	No pediatric concerns reported. However, reduced prolactin levels by dopamine may reduce milk production[15]
	Pramipexole	Based on studies in rats and rabbits, an increase in malformations is not anticipated in women treated with pramipexole during pregnancy.[14] Human safety data are limited to case reports and case series but do not show evidence of malformations	No information is available on the use of pramipexole during breastfeeding, but it suppresses serum prolactin and may interfere with breastfeeding, therefore this medication is not recommended with breastfeeding[15]
	Ropinirole	There are no human data. Based on experimental animal studies, ropinirole is not expected to increase the risk of congenital anomalies[14]	No human studies are available concerning levels in milk. Medication might inhibit lactation because of its prolactin lowering effects, therefore, this medication is not recommended with breastfeeding[15]
Opioids	Oxycodone	Neonatal withdrawal after maternal use has occurred with opioid medications. Oxycodone use in the first trimester was associated with an increase in pulmonary valve stenosis in one retrospective study. These findings were not confirmed in other studies[14]	Small amounts are secreted in breast milk. Sedation of the newborn may be observed[15]
	Codeine	Based on experimental animal studies, codeine use during pregnancy is not expected to increase the risk of congenital anomalies. Reports of malformations in humans after pregnancy exposure to codeine have been inconsistent. Neonatal withdrawal may occur after late pregnancy use of codeine. Rapid metabolism of codeine is a genetic characteristic that may lead to dangerous milk levels of morphine in a minority of women[14]	The amount of codeine secreted into milk is low and dose-dependent. Infant response is higher during neonatal period (first or second week). Observe baby for sedation and constipation[17]
Antihypertensive	Clonidine	Based on experimental animal studies, clonidine use during pregnancy is not expected to increase the risk of structural malformations. Effects of pregnancy exposure on offspring behaviour have been suspected based on human experience and experimental animal studies[14]	Clonidine is minimally excreted in human milk. No pediatric concerns reported, but newborns may need to be observed for hypotension. Clonidine may reduce milk production by reducing prolactin secretion[17]

Note: RLS: restless leg syndrome.
Adapted from original.[19]

hygiene and medications associated with RLS when possible. Nonmedication treatments such as lower extremity stretch and massage, elastic compression stockings, warm baths and moderate regular exercise should be endorsed. When medication is needed in pregnancy, the risks and benefits of treatment should be discussed with the patient. Due to the ethical concerns of enrolling pregnant patients in drug trials, safety data in pregnancy is primarily based on animal studies or on retrospective case control or cohort studies. The U.S. Food and Drug Administration's (FDA's) pregnancy categories may be used as a summary guide of available data. However, the FDA categories cannot replace thoughtful consideration of a particular medication's history and pharmokinetics and the stage of pregnancy in which the medication is administered. Useful sources of updated information on drug safety during pregnancy and lactation include Reprotox,[14] LactMed[15] and other reference guides.[16,17] If iron or folate deficiency is identified, appropriate therapies such as iron replacement or folate replacement can be instituted. In the rare event that oral iron supplementation is not adequate, intravenous iron can be given in the form of iron sucrose or ferric carboxymaltose.[20]

For those patients who either do not have iron or folate deficiency or do not respond to replacement therapy, other agents such as clonidine, opioids and benzodiazepines may be considered, although they are not considered first-line therapy in the 2012 American Academy of Sleep Medicine practice parameters.[17] Table 3 outlines some current medications available for RLS and the available safety data in pregnancy and nursing. Newborns exposed to medications in utero, especially opioids and benzodiazepines, should be observed closely for respiratory depression and withdrawal.

Conclusion

Restless Leg syndrome is a common complaint in pregnant women. The common symptoms of RLS include an urge to move the limbs, unpleasant sensations in the legs that are relieved with movement, and these are worse in the evening. Pregnancy increases the chance of having RLS due to hormonal issues as well as iron deficiency and folate deficiency. Treatment of RLS is usually to supplement iron and folate. If that is not helpful, standard medications for RLS can be used and those are reviewed in detail in this article.

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Ethical Approval

The patient consented to her information being used in this manuscript.

Guarantor

CD

Contributorship

All authors contributed to, reviewed and edited the manuscript, and approved the final version of the manuscript.

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